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PROCEEDINGS OF THE ASSOCIATION OF ECONOMIC BIOLOGISTS

Ordinary meeting held at 2.30 p.m. on May 13th, 1927, in the Imperial College of Science. The President, Mr J. C. F. Fryer, M.A., in the Chair.

DISCUSSION ON PLANT ALKALOIDS.

I. "The Principal Plants yielding Alkaloids" by Lieut.-Colonel A. T. Gage, C.I.E., lately Director, Botanical Survey of India, and Superintendent, Royal Botanic Gardens, Calcutta.

II. "The Biochemistry of the Alkaloids" by Dr T. A. Henry, Director, The Wellcome Chemical Research Laboratories.

III. "The Medical Aspects of the Alkaloids" by Dr J. Trevan, The Wellcome Physiological Research Laboratories.

IV. General Discussion—Mr Fryer, Dr Pethybridge, Mr Howes, Dr Henry, Dr Trevan.

I. THE PRINCIPAL PLANTS YIELDING ALKALOIDS.

By Lieut.-Colonel A. T. Gage, C.I.E., M.A., M.B., B.Sc.
(*Late Director, Botanical Survey of India, and Superintendent, Royal Botanic Gardens, Calcutta.*)

Major Chipp in his letter in which he conveyed his honourable invitation for me to take part in this alkaloidal symposium had the following remark: "We should not trespass on your time for more than twenty minutes." In this there was an obvious transposition of the pronouns, for he should have written "You should not trespass on our time for more than twenty minutes." Anyhow I hope I shall not much exceed that limit.

Fortunately for you and me I am not called upon to say anything about alkaloids themselves. I am merely the showman pointing to the pictures with more or less appropriate patter, to whet your appetite for the real performance, when Drs Henry and Trevan put their trained troupe of alkaloids through their paces.

I may just confide in you my personal impression of the rarity of alkaloids in their unadorned beauty. We consume incredible quantities of tea, coffee and tobacco, but how many of us have ever seen Caffeine or Nicotine. For half of every year for many years I lived amidst miles of Tea and Cinchona plants, but only on one occasion have I been introduced to Caffeine and Quinine, when the Government Quinologist showed me two phials, one of which, he said, contained Caffeine from tea-prunings and the other Quinine. I inspected them with the reverential care they seemed to call for and handed them back to him. Since then I have seen no other.

As within the time at our disposal only a limited number of the regiment of alkaloid-yielding plants can be inspected, the selection of those to file past leaves

room for difference of opinion according as to whether the arranger of the inspection is an economic biologist, a pure chemist, a pharmacologist, a physiologist, a physician, a grocer, a tobacconist or an artist in poisoning.

Although it is possible that not all of these are represented here, there is probably enough of different interests to make the selection somewhat of a problem. Being unfortunately precluded from adopting one of the bright modern methods of simultaneously raising money and gaining information by inviting you to participate on the usual terms in an "Alkaloid Ballot," I have fallen back upon a method of the B.B.C. who occasionally broadcast a programme arranged by an outsider according to his individual taste. So as one who is, or rather was, a mere systematic botanist, I have made out my own list with an equitable disregard of everyone else's interest. The question of the relative importance of alkaloids is as far as I am concerned evaded by passing the plants along in the order of the natural families to which they belong. At the risk of trespassing on Dr Henry's province, it may be mentioned here that when, as the slides are passing along, only one alkaloid is mentioned in connection with a plant it is not to be inferred that the plant contains no others. Further, when roots, seeds, bark or other parts are mentioned as the source of alkaloids, it means merely that the alkaloids are usually or most conveniently extracted from such parts. Finally such expressions as root or seed or bark and suchlike are extremely crude indications of how the protoplasm of a plant disposes of the alkaloids it produces in the course of its metabolism.

Lantern slides were then shown of the following plants, the lecturer commenting upon each.

1. ACONITUM NAPELLUS L. (Ranunculaceae), the familiar Monkshood of our gardens, is taken as the representative of a genus widely distributed over the Northern Temperate Zone. Most of the species store alkaloids, chiefly in the root, and several of these alkaloids are very poisonous. The typical alkaloid is Aconitine.

2. BERBERIS ARISTATA DC. (Berberidaceae) is a spiny evergreen shrub, a native of the Himalayas and the hills of Southern India and Ceylon and cultivated in this country as an ornamental shrub. The thin brittle root-bark more particularly yields *Berberin*, an alkaloid that occurs in a considerable number of other species, some belonging to the same genus, and others to different families.

3. PAPAVER SOMNIFERUM L. (Papaveraceae), the opium poppy, is probably a native of S.E. Europe and Asia Minor, but cultivated in Asia Minor, Persia, India still to a small extent, and China. The milky juice, which is collected by incising the capsules, is a fount of different alkaloids, over a dozen occurring in the stream. The chief one is of course Morphine.

4. CAMELLIA THEA (Ternstroemiaceae). The tea plant is native to Assam and extensively cultivated in that province, the Eastern Himalayas, Southern India, Ceylon, Java, China and elsewhere in the Tropics and Sub-tropics. It contains the most widely consumed of all alkaloids in the form of caffeine, which is usually extracted from the leaves.

5. THEOBROMA CACAO L. (Sterculiaceae). The cocoa plant is a small tree, a native of the northern parts of South America and up to as far north as Mexico. Extensively

cultivated in the tropics. The alkaloid Theobromine is the substance in the seeds which, along with the concrete oil, gives the flavour to the beverages that Linnaeus considered such divine liquors that he called the genus Theobroma, the Food of the Gods.

6. ERYTHROXYLON COCA Lamk. (Linaceae), the source of Cocaine, is a shrub extensively cultivated in the northern Andes and also in Brazil and other South American countries. The alkaloid that is extracted from the leaves reminds me that I might have included detectives in the list of the interested ones, as it is probably better known by repute than any other alkaloid to the ordinary man from its association with Sherlock Holmes in literature and Scotland Yard in newspaper reports of the activities of "snow" smugglers.

7. PILOCARPUS PINNATIFOLIUS Lemaire (Rutaceae), from the leaves of which the alkaloid Pilocarpine is obtained, is a shrub of Brazil. The leaves are compound, a foot or more long, with 2–5 pairs of 3–4 in. long leaflets and a terminal one. The inflorescence of long spiciform erect racemes, bearing numerous shortly pedicelled small reddish purple flowers.

8. PHYSOSTIGMA VENENOSUM Balf. Calabar Bean. A large leguminous climber, a native of Old Calabar, but introduced into Brazil and India. The seeds contain the well-known alkaloid Physostigmine or Eserine, very poisonous.

9. CONIUM MACULATUM L. (Umbelliferae). Hemlock. This herb has a wide distribution throughout Europe to temperate Asia and North Africa and has been introduced into both North and South America.

The species harbours several alkaloids. In poisonous doses the mind remains unaffected to the last, the classical instance of this being the death of Socrates as related so movingly by Plato in the *Phaedo*.

10. CINCHONA LEDGERIANA, C. OFFICINALIS and C. SUCCIRUBRA (Rubiaceae). Trees native to the eastern side of the Andes and introduced some 60 years ago into Java and India. They contain several alkaloids, the most important from the commercial and medical point of view being Quinine. The most important species is *C. Ledgeriana*, by far the most extensively cultivated.

11. COFFEA ARABICA and other species (Rubiaceae). A shrub or small tree native to tropical Africa, but widely cultivated in the tropics. The characteristic alkaloid obtained from the seeds is Caffeine, which occurs also in Tea, Paraguay Tea (*Ilex paraguayensis*), Kola and other species.

12. PSYCHOTRIA IPECACUANHA (Rubiaceae). A small shrub, a native of the tropical forests of Brazil, but cultivated in other parts of the tropics. It is cultivated to a small extent in India and still more in the Malay Peninsula.

Emetine, the alkaloid so useful in one form of dysentery, is contained chiefly in the root bark.

13. STRYCHNOS NUX VOMICA L. (Loganiaceae). A moderate sized tree, native to India, Ceylon, Burma, Cochin-China and parts of the Malay Archipelago.

The seeds yield several alkaloids, the chief being Strychnine. Taste is very bitter.

CURARINE got from other species of Strychnos.

14. NICOTIANA TABACUM L. (Solanaceae). A coarse annual. Probably a native of Central or South America.

The leaf alkaloid is a volatile liquid, Nicotine.

15. DATURA STRAMONIUM L. (Solanaceae). A coarse weedy annual. Spread throughout the world. Daturine from the leaves and seeds. Akin to Atropine.

16. ATROPA BELLADONNA L. (Solanaceae). A large bushy herb. Central and Southern Europe, South-west Asia and North Africa.

ATROPINE from the roots and leaves. Crystalline.

17. HYOSCYAMUS NIGER L. (Solanaceae). An annual or biennial herb. Temperate Europe and Asia. Introduced into America.

Hyoscyamine from the seeds and leaves.

II. THE BIO-CHEMISTRY OF ALKALOIDS.

By T. A. Henry, D.Sc. (London).

(*Director Wellcome Chemical Research Laboratories.*)

The first clearly defined alkaloid—morphine—was isolated in 1817, so that over a century has elapsed since the interest of chemists in these products was first evoked. During that period hundreds of new alkaloids have been discovered and described, and great progress has been made in the determination of their intimate structure. The precision which has been reached in some branches of work of this kind may be gauged from the fact that last year conclusive proof of the constitution of the rare opium alkaloid, codamine, was furnished by Prof. E. Späth of Vienna by the use of only 0·2 gm. of the original specimen of this alkaloid isolated from opium by O. Hesse in 1870.

The constitutions of quinine and the more important related alkaloids derived from cinchona have been known for some years, and syntheses of this group of alkaloids cannot now be long delayed. The structure of all the commoner alkaloids of opium is known, with the exception of the most important of all, viz. morphine and its close relatives, codeine and thebaine, and here only details remain to be settled. Similar progress is being made with other alkaloids of special therapeutical interest such as emetine and strychnine, and the activity in alkaloidal research at Manchester, Oxford, Marburg and Vienna is such that one wonders how long the known supply of "alkaloids of unknown constitution" will hold out. The organic chemist can reasonably claim that he has done his part in adding to the knowledge of alkaloids, but it is of interest to note that in spite of all this activity no natural alkaloid has yet been replaced commercially by its synthetic equivalent, though this could be done in a number of cases if necessity for it arose. The fact that man is still dependent on natural sources for supplies of these indispensable medicinal products makes it all the more surprising that next to nothing is known of the part they play in the physiology of plants. This lack of knowledge is no doubt due to the facts that the most important alkaloidal plants are grown in the Tropics, where facilities for bio-chemica research are still severely restricted, and that, except in the cases of cinchona and

opium, production is scattered and on a small scale, so that there is no organisation for the systematic research necessary to secure such information. Alkaloidal plants, such as those of the Solanaceae and the Leguminoseae are however available in temperate regions, and the numerous problems presented by the distribution, origin and function of alkaloids in plants will no doubt eventually attract the attention of the bio-chemist. At present the bio-chemistry of alkaloids consists of little more than casual, unrelated observations with much, more or less, plausible speculation.

Alkaloids may be defined as naturally occurring, relatively complex, basic substances usually exhibiting marked physiological action, but the term is not always used in this strict sense outside chemical circles. It is not uncommon to find the name applied to such substances as digitoxin, strophanthin and santonin, that is, to naturally occurring, physiologically active substances, which contain no nitrogen and are not basic. That is the essential difference and, broadly speaking, alkaloids are classified for convenience of description according to the way in which the constituent nitrogen is built into the molecule. The simplest alkaloids are derivatives of open chain or aliphatic amines, whilst the more complex have as nuclei, closed heterocyclic chains in which the nitrogen is the heterogeneous element. The more complex alkaloids are further subdivided, according to the nature of these heterocyclic rings into derivatives of pyrrolidine, piperidine, glyoxaline, etc., and still further according to the nature of the proximate structure of which the primary heterocyclic ring forms part, into tropane, granatane, quinuclidine, quinoline, isoquinoline, indole, purine etc., derivatives. Such schemes of classification become increasingly difficult as knowledge of the structure of alkaloids grows and though they are always misleading something of the kind is necessary for purposes of general discussion.

Taking a group of plant species so closely related as to be included in one natural order, it is reasonable to assume that the plants concerned will possess a common metabolism and have most of their characteristic constituents in common. That seems to be true as regards alkaloids in only one natural order, viz. Amaryllidaceae in which the characteristic alkaloid is an *iso*quinoline derivative, lycorine or narcissine which has been found in at least ten genera of the order. It is also true of such a characteristically alkaloidal order as the Papaveraceae where in spite of the many different alkaloids that may be present in a single plant—there are at least 25 in the opium poppy—all are *iso*quinoline derivatives, so far as is known, and all can be regarded as arising by a common process.

A more usual state of things is presented by such orders as the Solanaceae and the Leguminoseae. In the former three well-defined and distinct groups of alkaloids occur, typified by hyoscyamine (tropane nucleus), nicotine (piperidylpyrrolidine nucleus) and solanine (a complex alkaloidal glucoside of unknown constitution) respectively. Hyoscyamine occurs in several genera, Datura, Atropa, Scopolia, Duboisia and Hyoscyamus, nicotine in one only, Nicotiana, whilst the solanines are found only in Solanum species.

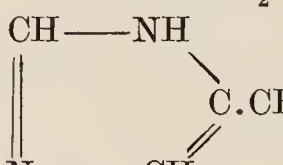
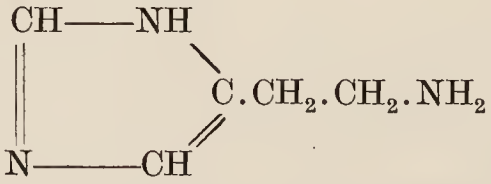
Much the same state of things is found in the Leguminoseae where cytisine (quinoline condensed with pyrazine or pyrazole as a nucleus) is the most widely distributed alkaloid having been found in *Anagyris*, *Baptisia*, *Cytisus Laburnum*, *Euchresta*, *Genista*, *Sophora* and *Ulex*. The alkaloid sparteine, which is a quinuclidine derivative, a characteristic which it shares with the principal cinchona alkaloids, is found in the genus Lupinus and in one species of *Cytisus* (*C. scoparius*). Trigonelline,

a simple pyridine derivative, is found in *Trigonella* and in *Pisum*. Hypaphorine and eserine, respectively simple and complex derivatives of indole occur in *Erythrina hypaphorus* and *Physostigma Venenosum*. Finally vicine, probably a purine glucoside, occurs in *Vicia* spp. and there are less well-defined alkaloids in other genera of the order. In view of this variation in the type of alkaloid, which may occur within a single natural order or even within a genus, as in *Cytisus*, it seems clear that by whatever process alkaloids may be formed in plants, it must be a process which from similar materials must be capable of giving rise to a variety of products.

None of the alkaloids so far mentioned are to be found in plants of more than one natural order, but berberine, one of the best known of the *iso*quinoline alkaloids, has been recorded in at least 14 genera belonging to five natural orders, Ranunculaceae, Berberidaceae, Menispermaceae, Papaveraceae and Rutaceae.

It is common ground with authors, who have put forward suggestions as to the mode of origin of alkaloids in plants that the primary materials must be amino-acids, produced by the breaking down of proteins, but it is at least equally probable that they are formed as by-products in the building up of proteins. The former process can be demonstrated, so far as the production of simple bases—too simple to be regarded as alkaloids—is concerned from what is known regarding the hydrolytic products of gliadin, one of the proteins found in rye and the amino-acids and amines found in ergot of rye and presumably produced by the action of this fungus on the proteins of rye grain. As shown in the following table, the six amino-acids from leucine to lysine are all found among the hydrolytic products of the gliadin of rye, whilst in the fungus the same animo-acids are represented by the corresponding amines, *iso*amylamine to cadaverine, produced in each instance by decarboxylation of the amino-acid, of which in most cases some also survives in the fungus.

Simple Bases of Ergot of Rye.

1.	Leucine	$CHMe_2.CH_2.CH(NH_2).COOH$	in rye and ergot
	*iso*Amylamine	$CHMe_2.CH_2.CH_2.NH_2$	in ergot
2.	Aspartic acid	$COOH.CH_2.CH(NH_2).COOH$	in rye and ergot
3.	Histidine		in rye and ergot
	Ergamine		in ergot
4.	Tyrosine	$HO.C_6H_4.CH_2.CH(NH_2).COOH$	in rye and ergot
	Tyramine	$HO.C_6H_4.CH_2.CH_2.NH_2$	in ergot
5.	Arginine	$NH_2.C(NH).NH.CH_2.CH_2.CH_2{\cdot}CH(NH_2)COOH$	in rye
	Agmatine	$NH_2.C(NH).NH.CH_2.CH_2.CH_2.CH_2.NH_2$	in ergot
	Putrescine	$NH_2.CH_2.CH_2.CH_2.CH_2.NH_2$	in ergot
6.	Lysine	$NH_2.CH_2.CH_2.CH_2.CH_2.CH(NH_2).COOH$	in rye
	Cadaverine	$NH_2.CH_2.CH_2.CH_2.CH_2.CH_2.NH_2$	in ergot

This sort of process gives us no clue to the origin of the real alkaloids, ergotoxine and ergotamine, found in the fungus and to which there is nothing analogous among the constituents of rye grain or their hydrolytic products.

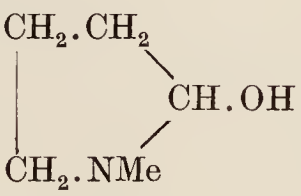
Of all the suggestions that have from time to time been put forward to account for the formation of alkaloids the most useful is that published by Robinson in 1917. These views have the great advantage that they postulate the pre-existence in the plant of nothing not known to occur there, or at any rate not likely to be present, they assume only the possibility of reactions, which there is every reason to believe do occur in plants, and Robinson has himself shown by the synthesis of tropinone and pseudo-pelletierine in the laboratory by these processes, that the latter can take place at atmospheric temperature.

On the basis of these views the following explantion of the formation of hygrine, the simplest alkaloid found in coca leaves is given.

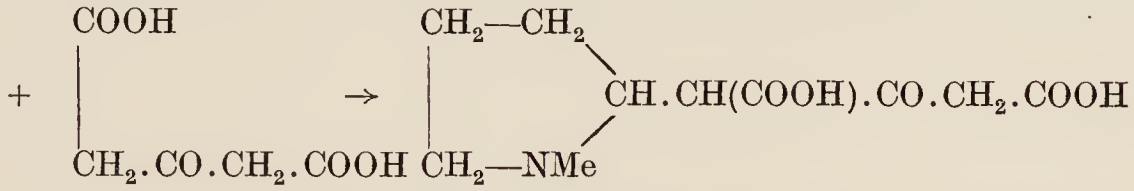
Stage I. Oxidation and methylation of ornithine by formaldehyde to a carbinolamine of the pyrrolidine series.

$$NH_2.CH_2.CH_2.CH_2.CH(NH_2).COOH + H.CHO \rightarrow$$

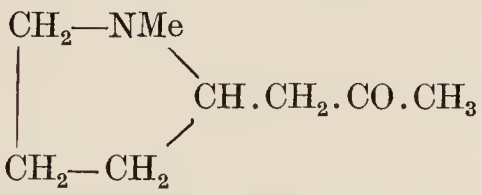
$$NH_3 + CO_2 + NHMe.CH_2.CH_2.CH_2.CHO \rightarrow$$



Stage II. Condensation of the carbinolamine with acetonedicarboxylic acid.



Stage III. Decarboxylation of the condensation product to (in this case) hygrine.



By a similar condensation of two molecules of the carbinolamine with one molecule of acetonedicarboxylic acid, a base isomeric with cuskhygrine would be produced, whilst, if Stage I is carried a step further, ornithine might yield succindialdehyde and methylamine, thus:

$$NH_2.CH_2.CH_2.CH_2.CH(NH_2).COOH + 2H.CHO \rightarrow$$
$$2NH_2.CH_3 + CO_2 + CHO.CH_2.CH_2.CHO$$

and from these two substances and acetonedicarboxylic acid, Robinson has shown that tropinone can be produced in the laboratory, and tropinone is a probable intermediate in the production of tropine and eventually of hyoscyamine in the plant.

Still keeping to the same materials, ornithine and acetonedicarboxylic acid, it is possible to represent by reasonable variations in the same processes the formation of nicotine, thus affording an explanation of the apparent anomaly referred to above that plants so closely related as to be placed in the same natural order Solanaceae may produce what at first sight appear to be totally different types of alkaloids, viz. hyoscyamine and nicotine.

There has thus been produced on the chemical side a promising view, supported by experimental evidence, of the processes by which even the most complex alkaloids known could originate in plants, and it now remains for plant physiologists and bio-

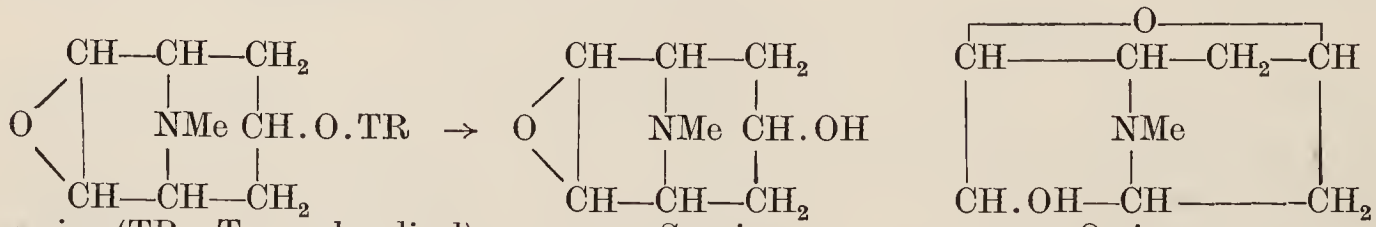
chemists to take up the subject from the biological side and prove or disprove the validity of Robinson's suggestions.

There is one other problem in connection with the bio-chemistry of the alkaloids, which must be referred to. The importance of alkaloids to man is obvious but their value to the plants which produce them is not so clear. Three views have been held as to their function in plants:

(*a*) that they are produced as protective agents,
(*b*) that they are plastic products destined for further use by the plant,
(*c*) that they are merely accidental products of metabolism, that is, waste products.

The first view has all the appearance of having been put forward without serious consideration. If toxic constituents protect plants, animals must be aware that such plants are dangerous and avoid them. There is however no evidence that this happens. Scarcely a year passes in which cattle are not poisoned in England by eating branches of the yew tree, and in countries like Australia, South Africa, and New Zealand where toxic plants have not been largely eliminated from the pastures by generations of careful farming, as they have in England, such plants cause serious annual losses to the pastoralist.

No experimental evidence of great value has been put forward for the view that alkaloids serve as plastic products, in the sense that they are used up by the plant iberating stored energy and being reduced to simple degradation products, but the sounder part of this view, suggested by Bayliss, that alkaloids may serve as stimulants of some kind has never been tested experimentally. It has been applied, with more reason perhaps, by Armstrong to certain of the glucosides, and it should not be overlooked that more alkaloids may occur in plants in the form of glucosides than is at present suspected. At first sight the fact that alkaloids are relatively stable and not highly reactive substances under the conditions obtaining in plants, whereas those glucosides which Armstrong regards as means of storing stimulants, produce on hydrolysis highly reactive substances, discounts the view that alkaloids can fulfil such a function, but it is interesting in this connection to remember that Willstätter has shown recently that the alkaloid hyoscine when hydrolysed by the pancreatic lipase yields the labile substance, scopine, which very readily passes into the stable substance oscine long familiar as the hydrolytic product of hyoscine, when the hydrolysis is brought about by acids or alkalis.



However that may be, the bulk of alkaloid found in any particular plant appears normally to behave as would be expected of a product formed accidentally and without ulterior purpose. It is typical of reactions with organic materials, whether produced by chemical or biological agency, that they are rarely complete or proceed wholly in one direction, and it is to be expected that in the synthesis of proteins from simple amino-acids some by-products will be formed, and that in the degradation of proteins reactions will occur between the amino-acids produced and other substances present in the plant at the same time. When metabolism is active the quantity of

these by-products formed is certain to increase just as the dump-heaps of a blast furnace grow with increased output of metal. It is often carelessly argued that alkaloids, tannins and other normal secondary constituents of plants must be plastic products because their amount is greatest when metabolism is most active but the fact is that real plastic products should be difficult to find when metabolism is most active, because they must be constantly used up and it is only when metabolism slackens that they should begin to accumulate. Perhaps the most convincing piece of work so far accomplished bearing on the function of alkaloids in plants was published by Dr H. E. Annett in India in 1921. He showed quite clearly that in the opium poppy, where the alkaloid-yielding latex is found in the walls of the unripe capsule, that neither the application of nitrogenous manures nor any change in environment affected the proportion of morphine found in the latex, though the quantity of latex formed might be so influenced. In a well-regulated factory one would expect the proportion of waste product to remain constant and the total quantity to increase or diminish as the environment was favourable or unfavourable to factory operations.

Annett also found that in lancing capsules for opium the whole of the morphine was removed in the first few lancings, later lancings yielding latex free from morphine. Further, the seed produced from lanced capsules was as good in quality as that formed from unlanced capsules, so that the latex does not appear to fulfil any special function in connection with the seed during the ripening of the capsule. In addition to special evidence of this kind, the general conditions under which alkaloids are produced and stored in plants, support the view that they are waste products.

Alkaloids are not as a rule found in quantity in seats of active metabolism, such as the leaves, except in short-lived plants where other means of storage are not readily available and even in these cases they are eventually transported to the rinds of the fruits as in the opium poppy, to the coats of the seeds as in some of the solanaceous plants or to the roots as in biennial plants. In perennial plants the usual source of alkaloids is the bark or the seeds, and in the latter, for example in Strychnos, strychnine and brucine are found mainly in the seed coats, which are thrown off and the alkaloids lost when the seed germinates.

III. THE MEDICAL ASPECTS OF THE ALKALOIDS.

By J. W. Trevan.

(*The Wellcome Physiological Research Laboratories, Beckenham, Kent.*)

The number of alkaloids which are used in medicine is small compared with the number known. Out of some 800 alkaloids described in Henry's *Plant Alkaloids* only comparatively few have a certain place in therapeutics. There have been, of course, claims that a very large number of extracts containing alkaloids have valuable therapeutic effects, but the number of alkaloids for which there is both scientific evidence from the laboratory, and a consensus of reasonable clinical opinion that they are valuable is about 27. There are many preparations which the increase of therapeutic scepticism in the latter part of the nineteenth century swept out of use, but I think the alkaloids enumerated below probably will be retained in scientific medicine for some time to come. Two indeed have only recently been introduced into general use—sparteine and ephedrine—and I think it is likely that new alkaloids or new uses

for old alkaloids will increase the list still further. The scientific evaluation of the therapeutic properties of a drug on man is an operation of extreme difficulty, much more difficult than its preliminary examination in the laboratory.

Alkaloids used in medicine may be divided into two groups, one producing specific effects on parasites infesting the body, the other producing physiological changes in the body which counteract the disturbances of function set up by disease of rendering possible certain therapeutic procedures involving interference with body functions. In the first group are the drugs given in Table I.

Table I.

Alkaloids having an antiparasitic action.

Alkaloid	Use
Quinine group	Destruction of malarial parasites
Emetine	Destruction of *Amoeba histolytica* (dysentery)
Conessine	Destruction of *Amoeba histolytica* (dysentery)
Pelletierine	Anthelminthic
Arecoline	Anthelminthic.

There are a few other alkaloids to which antiparasitic properties have been attributed but the evidence is not conclusive.

The alkaloids of the second group can be subdivided according to their site of action.

(1) Drugs used for their Action on the Central Nervous System.

A. *Depressants.*

1. *Morphine* is the oldest member of this group. It produces its principal effect in the body by diminishing the activity of the cerebrum. It is probably still the most valuable drug for this purpose. Nothing approaching the effect of morphine is produced by any of the modern synthetic hypnotics which pour out in a vast spate year by year from Continental chemical laboratories. The sleep produced by morphine is a nearer approach to natural sleep than any other drug produces. After taking the ordinary hypnotic the patient generally awakes with a headache comparable to that "morning after the night before" sensation which succeeds the sleep produced by over-indulgence in alcohol—which of course is the physiological type of the synthetic hypnotics. This unpleasant effect is absent after morphine and probably because of this very fact morphine is more prone to give rise to the drug habit. I feel that it is illogical to suppose that by any synthesis a drug will be produced equivalent to morphine in therapeutic effect but not prone to give rise to the drug habit. After all the foundation of the drug habit must really depend on the efficacy of the physiological effect produced. The morphinomaniac started his habit because of the therapeutic effect of the drug. Morphine also has a special action where sleeplessness is produced by pain. Much larger doses of the synthetic hypnotics have to be given where there is any great pain. This suggests that morphine has a special action on the ganglia in the base of the cerebrum which are specially concerned with the reception of sensory impulses, and indeed there is evidence from the reaction of the cat that the highest centres in the cerebrum are stimulated by morphine in small doses. Pain at any rate disappears before consciousness is affected when morphine is

administered, whereas the highest part of the cerebrum is put out of action first by hypnotics. Morphine and its derivative heroin are also valuable for their power of diminishing cough by depressing reflex excitability.

2. *Hyoscine* is also used for its depressant effect on the cerebrum. It is used in acute mania. Morphine is not much good in this connection—which is evidence in favour of the suggestion outlined in the last paragraph as to the action of morphine on the cerebrum. Hyoscine has the disadvantage of having certain peripheral effects on the pupil and the secretory glands similar to that of atropine. The peripheral action of atropine is due almost entirely to the laevo-hyoscyamine which it contains. The optical isomer dextro-hyoscyamine, the other constituent of atropine, has no such peripheral action and we are trying it at the moment as a substitute for hyoscine, but the results are not complete.

B. *Stimulants.*

The most important alkaloid used for stimulating the central nervous system generally is *strychnine*, which acts on all parts of the central nervous system, increasing the rapidity with which the organism responds to sensory stimuli and diminishing the latent period of reaction. It is almost confined to uses as a general tonic.

One alkaloid has recently found a place in therapeutics because of its more or less selective activity on the part of the central nervous system which is responsible for the regulation of respiration, namely *lobeline*, which stimulates respiration in a very striking fashion.

Apomorphine stimulates the vomiting centre.

Caffeine also has a stimulating effect on the cerebrum. I have seen acute mania develop as a result of caffeine poisoning, and we all know its effect in the form of tea.

(2) Drugs Acting on the Peripheral Nervous System.

A. *On the involuntary nervous system.*

The alimentary tract, the vascular system, the secreting glands, the sweat glands, the muscle of the eye and various other structures are under the control of two sets of nerve fibres which in general have opposing effects on these structures. One set of these fibres goes by the name of the *sympathetic system*, and the other by the name of the *autonomic nerve system*.

(*a*) *Drugs acting on the sympathetic system.*

Stimulants. The body itself produces an alkaloid which is concerned with the stimulation of the sympathetic system, namely *adrenalin*. There is only one alkaloid which has found extensive application in therapeutics for its effect on the central and sympathetic nervous system, and that is *ephedrine*, which has an action very similar to that of adrenalin. Its chemical formula is somewhat similar (see Fig. 1). It acts just like adrenalin by increasing the pulse rate, increasing the extent of the contraction of the heart, raising the blood pressure by causing contraction of the smooth muscles of the walls of the arterioles and it dilates the bronchioles. It is much more stable than adrenalin because of the absence of hydroxyl in the phenyl group. Larger doses have to be used of it than of adrenalin, but it can be administered by mouth whereas adrenalin is almost without action when taken by mouth probably because it is destroyed before it is absorbed. The drug comes from a species of *Ephedra* found in China and records of its use are said to be in existence dating from 5000 years ago.

It seems likely that this drug will find great usefulness in the treatment of asthma, the immediate cause of which is a spasmodic action of the bronchioles. An adequate

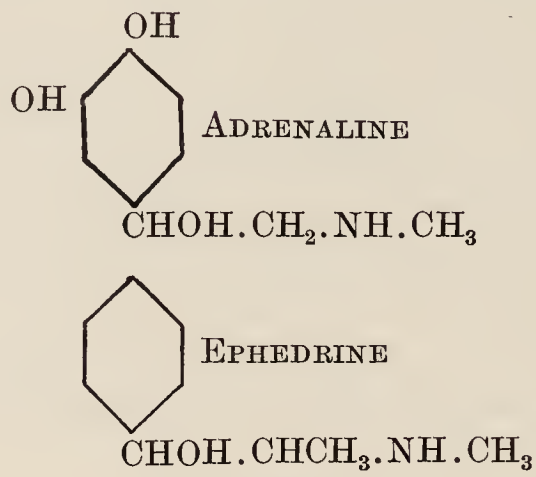


Fig. 1.

dose of ephedrine given by mouth relieves the condition in a few minutes in most cases. Other drugs which stimulate the sympathetic that are found in plants are *hordenine* and *tyramine* but they are very little used in therapeutics.

(*b*) *Drugs acting on the autonomic system.*

The belladonna group of alkaloids are most important in this connection. *Atropine* is the most important drug. It is made up as already stated of equal quantities of dextro- and laevo-hyoscyamine of which the laevo- is the most active on the autonomic system. It is used principally for dilating the pupil and paralysing the accommodation of the eye, as for instance, when the oculist wishes to examine the retina or measure the optical constants of the refractive media of the eye. It has been to some extent superseded by a synthetic product *homatropine* but its use is still necessary where prolonged action is required or for children. It is also used in relaxing the bronchioles in asthma and bronchitis by paralysing the constrictor fibres which are supplied by the autonomic system. Children are very tolerant of the drug. It has occasional uses in paralysing the nerve endings of the secretory glands and is used as a test in typhoid fever in which an injection of atropine fails to cause a rise in pulse rate as in the normal human. The autonomic fibres which supply the heart through the vagus nerves are continually in activity in the normal animal, keeping a pulse rate lower than it had otherwise been. Atropine paralyses these nerves and so increases the pulse rate. In typhoid fever normal activity of the vagus is in abeyance. The vagus nerve also supplies the intestine so that the paralytic effect of atropine makes it good for colic.

Physostigmine stimulates the autonomic nerve endings, causing contraction of the pupil and exaggeration of the movements of the bowel. Its uses in medicine are to counteract the effect of atropine after an optical examination and to stimulate a paralysed bowel to contract after surgical operations.

Pilocarpine is the other alkaloid which is used for its effect on the autonomic system. It is principally used for producing sweating in kidney disease.

B. *Drugs that act on the sensory nerve endings.*

Aconite has a reputation for producing anaesthesia when applied in the form of an ointment to the skin. It is a highly dangerous drug which is going out of use.

The most important alkaloid which acts on the sensory nerve endings is of course

cocaine. It is still the best local anaesthetic available for ophthalmic purposes and for the nose and throat. It has the advantage over all the local anaesthetics so far proposed as substitutes, of causing constriction of the pupil and constriction of small blood vessels both of which properties make it indispensable for use in ophthalmic work. The various substitutes synthesised in the laboratory are displacing it in other fields, but the eye surgeon still depends on it.

(3) Drugs Acting on Muscle.

A. *Heart muscle.*

Caffeine is used as a cardiac stimulant but not extensively.

Quinidine and *sparteine* are used for their depressant action on the heart muscle. There is a clinical condition known as auricular flutter, the principal symptom of which is a very rapid pulse rate and consequent embarrassment of the circulation. The administration of either of these drugs reduces the pulse rate abruptly to normal by an action which has been worked out in detail by Sir Thomas Lewis and his colleagues.

B. *Involuntary muscle.*

The work of Macht has shown that *papaverine* inhibits the contraction of smooth muscle. The discovery of this property has led to the use of this alkaloid in the various forms of colic which are produced by spasmodic contractions of organs containing smooth muscles.

There are a certain number of alkaloids which are used for their stimulating effect on the muscle of the uterus namely *ergotoxin* (and the closely allied *ergotamine*) which is used to produce contraction of the uterus after labour, and *hydrastine* and *cotarnine* which are used to prevent excessive menstrual haemorrhage.

The alkaloids used to stimulate the kidney to secrete are *caffeine* and *theobromine* principally, and they probably produce their effects by acting on the blood vessels.

The majority of alkaloids that are used in medicine are therefore used for their action in interfering with the normal mechanism of the body. Such a method of treatment is perhaps to be deprecated. It is rather like putting sand into a clock to regulate its time-keeping properties when the pendulum has dropped off. Unfortunately we cannot always find the missing pendulum when the body goes wrong and we have to do the best we can. It is extraordinary, and, I suppose, characteristic of living things how with a little assistance the body can get along with one or more organs permanently damaged. There is one interesting recent example of the condition in which the missing link which gives rise to disturbances of function has been prepared in a form in which it can be administered—the missing pendulum has been found. I refer to the condition of excessive menstrual haemorrhage. It is becoming fairly clear that this is due to a deficiency in a hormone which can be prepared from the ovaries of cattle. The excuse for retaining *hydrastine* in our list should therefore disappear, and the hope of the physician is that with the progress of knowledge more discoveries similar to this will render the use of alkaloids and other remedies for purely symptomatic treatment less and less necessary. With regard to the drugs in Table I the ground for their use is a much more logical one. Their action is directly on the exciting cause of a disease, and it seems possible that additions to the therapeutic armament of a physician will be members of this group rather than of the other. The discovery of new alkaloids with this type of action is of course much more

difficult than that of alkaloids in the other group. We may however take some encouragement from the fact that it is not many years since it was found that Bilharziosis, which is such a plague in Egypt, can be effectively treated by this drug. With the characteristic exasperation of therapeutic research, another specific for this disease, namely tartar-emetic, was discovered almost at the same time.

IV. GENERAL DISCUSSION.

CHAIRMAN: One of the questions raised by Dr Henry was the reason for these alkaloids in plants, and he mentioned the suggestion, though I do not think he proved it, that they might be protective. Plants run great risk from insects, and I think it can be said with certainty that the presence of alkaloids is no protection. I remember how greatly the seed and seed capsules of a poppy in Ceylon were attacked by a butterfly which ate them, and in this country the Hemlock has a moth that eats inside it. There is not much evidence that alkaloids are a protection.

One question I would like to ask is whether you (Dr Henry) think there is any prospect of replacing the plant as a maker of alkaloid. In my business, as an Economic Entomologist, we are very dependent on nicotine as an insecticide, but getting it from the tobacco plant is expensive, and if we could have nicotine replaced commercially, we think perhaps it would make a difference.

Dr PETHYBRIDGE: I should like to know if it holds good in most cases that manuring has no effect on the quantity of alkaloid developed. I remember trying to grow tobacco in Ireland, which could be smoked, and in our first efforts the proportion of nicotine was about something like 14 per cent., and the smoking of it was perfectly vile. We were told that the reason was that it had had too much nitrogenous manure, and certainly the fact was proved.

Mr HOWES: I should like to ask Dr Trevan why it is that any native races who make use of arrow poisons can eat the fish without fear of consequences; they use poisoned arrows for game and eat the flesh. Surely these things have alkaloids in them. Is it merely distributed all over the animal and dispersed in small quantities?

CHAIRMAN: One of the things which attracts one about all the alkaloids is how extraordinarily specific they are in their action. In the use of alkaloids as insecticides, it is found that one will be extraordinarily toxic, and a closely related one will have no action whatever. I assume that nicotine is present as nicotine in growing leaves of the tobacco plant, but in spite of that there are a large number of caterpillars which will live and flourish on these leaves, whereas if one gets the nicotine out and puts it on the outside, the caterpillar will eat it and die. It may be that the nicotine is not present in the plant but is produced by fermentation?

Dr HENRY: With regard to the synthesis of alkaloids, it is very unsatisfactory for a chemist to have to confess that although we have been at work on these things for a long time, there is not, at the present time, any case in which a natural alkaloid has been replaced commercially by its synthetic equivalent. The nearest approach is cocaine, which has been developed by Robinson's process, and sparteine has been put on the market, which is not a very good substitute. In the special case of nicotine, I do not think very much attention has been given to that, but it is a more promising

case. I think it should be possible to produce something, but what is proved is, that a good deal of work is needed. I think it is quite likely that if quinine were synthesised to-morrow we should be unable to put it on the market in competition with cinchona.

With regard to manuring, the only effect of manuring is to increase the yield of plants and to increase the amount of alkaloid in that way, but the quantity of alkaloid in a plant is not raised. The case in Ireland was not understood and has never been explained. It merely emphasises the necessity of more work being done on that side.

As to the form in which nicotine exists, what the Chairman suggests is quite likely. The method by which alkaloids are got out of the plant might destroy glucosides, and you could have it in some form which would not be toxic, but that is a point which wants investigating.

Dr Trevan: Both questions are difficult. As regards poisons—take for instance the arrow poison—the most important types are poisons which contain glucosides of a digitarious type. To begin with, the amount they get is very small, and though enough to kill the animal is nothing like enough to kill a man. You can kill a rabbit with less than a therapeutic dose. That is one way in which I think the native who uses arrow poison escapes. The other is that by the method of injection of poison under the skin the dose to kill an animal is considerably less than that taken by mouth. Another suggestion that has been raised, though I do not think there is any good evidence for it, has been advanced in the case of fish poison; it is said that the toxin accumulates in the brain and natives are very careful not to use the cerebrum (?).

As regards the specificity of alkaloids, that is a long question, and all I know is that it is a most amazing thing that two substances quite similar in structure put into an animal produce different results, whilst two unrelated substances may have quite similar physiological actions.